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# Pulmonary vascular changes in interstitial lung diseases

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## ABSTRACT

**Aims:** Pulmonary hypertension (PH) is commonly seen in patients with interstitial lung diseases (ILDs), and is associated with a worse prognosis. The aim of this study was to determine the prevalence of PH in patients with ILDs and identify the markers that may predict this complication without invasive procedures. For this purpose, the correlation between mean pulmonary artery pressures and diffusion test, functional assessments, such as six-minute walk test, was investigated.

**Methods:** The study group included 30 patients who were diagnosed interstitial lung disease between February 2010 and February 2011. Demographic and clinical characteristics, physiological studies, sixminute-walking test and high resolution computered tomography results were prospectively collected, and compared between patients with and without PH. Pulmonary hypertension was defined by right heart catheterization and results were compared between patients with PH and with non-PH.

**Results:** The study cohort consisted of 30 patients, of whom 14 patients (46.6%) had PH. When compared with non-PH subjects, patients with PH exhibited lower six-minutes-walk distance (415±41 m vs. 260±95 m, p<0.001), increased oxygen desaturation percentage during six-minutes-walk test (12.44±5,46 & 7.12±3.48), and decreased percentage of predicted FVC% (49±13.95 & 67±11.56), percentage of predicted FEV1% (52±13.2 & 73.5±12.43), and percentage of predicted DLCO% (38.8±13.7 & 65.3±11.23).

**Conclusion:** As a result, if there is a doubt about the decrease of pulmonary function tests and exercise capacity, patients with ILDs have to be investigated for pulmonary hypertension.

**Keywords:** Interstitial lung disease, pulmonary hypertension, six-minutes walk test, pulmonary functional tests

## INTRODUCTION

The development of pulmonary hypertension (PH) in the context of interstitial lung diseases (ILDs) is a well-known complication of various ILDs. The pathogenetic concepts of pulmonary fibrosis have interesting commonalities with the pathogenetic mechanisms responsible for the development of PH. As a result of epithelial damage occurring in interstitial lung diseases, oxidative stress occurs, fibroblast proliferation is stimulated as a result of the released cytokines, and angiogenesis and neovascularization inevitably occur as a result of restructuring.[1] Clinically, PH can produce dyspnea, fatigue, and exercise limitation, which are also characteristic symptoms of ILDs. As a result, PH may not be noticed in patients with ILDs until signs of right heart failure develop.[2] Echocardiogram (ECHO) is a valuable noninvasive technique for diagnosis and follow-up. Regurgitation of the pulmonary valve on ECHO, shortening of the right ventricular ejection acceleration time, dilatation in the right heart chambers, functional and structural deterioration in the interventricular septum, increase in right ventricular wall thickness, and dilatation in the main pulmonary artery suggest pulmonary hypertension. However, echocardiography has limitations depending on the method and the person evaluating it and cannot provide a definitive diagnosis of pulmonary hypertension.[3] The gold standard diagnostic method for monitoring the degree of the disease, arranging the treatment and ensuring the response to treatment is right heart catheterization and measurement of pulmonary artery pressure.[4]

The aim of this study is to identify markers that can predict the presence of pulmonary hypertension in ILDs without invasive procedures. For this purpose, the correlation

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between mean pulmonary artery pressures and diffusion test, functional assessments, such as 6-minute walk test (6MWT), was investigated.

## METHODS

Ethics committee approval was obtained from Eskişehir Osmangazi University Faculty of Medicine (Date: 31.08.2010, Decision No: 2010/165). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The data of 30 patients who applied to our chest diseases department between February 2010 and February 2011 and were diagnosed with interstitial lung disease and agreed to participate in the study were evaluated. The final diagnoses of the patients were reached after clinical, radiological and histopathological examinations. Fifteen patients diagnosed with idiopathic pulmonary fibrosis, five patients diagnosed with stage 4 sarcoidosis, three patients diagnosed with asbestosis due to environmental exposure, three patients diagnosed with hypersensitivity pneumonitis, one patient diagnosed with nonspecific interstitial pneumonia, one patient diagnosed with lung disease due to rheumatoid arthritis, and two patients diagnosed with pneumoconiosis were included in the study. All patients underwent arterial blood gas analysis, 6MWT, carbon monoxide diffusion test and pulmonary function test. Oxygen saturation of the patients was monitored with a pulse oximeter before and during the 6MWT. Desaturation during the test was recorded. To evaluate whether pulmonary hypertension developed, right heart catheterization was performed in all patients. Pulmonary arterial pressure of 25 mmHg and above was considered as pulmonary hypertension.

### Statistical Analysis

The data were analyzed using the SPSS 22 package program. Shapiro-Wilk test was used to determine distribution forms. Independent samples t-test was used to compare the means between groups. Yates Chi-square test was used to analyze cross-tables. ROC analysis was used to determine critical values, and specificity and sensitivity were determined. Stepwise logistic regression analysis (Backwardwald model) was used in the multivariate analysis of the data regarding the variables of 6MWT distance, desaturation during the test, expected FEV1%, expected FVC%, expected DLCO%, expected DLCO/VA% between the groups. Hosmer Lemeshow test were used to investigate the significance of the model. Data were summarized as mean±standard deviation. A value of $p<0.05$ was considered statistically significant.

## RESULTS

30 patients diagnosed with interstitial lung disease were included in the study. Final diagnoses of the patients; idiopathic pulmonary fibrosis (n=15), asbestosis (n=3), chronic sarcoidosis (n=5), chronic hypersensitivity pneumonia (n=3) and unclassifiable (n=4). 15 of the patients were women and 15 were men. The average age of women was 60.6 (±13.8) years, and the average age of men was 62.5 (±12.5) years. Pulmonary hypertension was detected in 14 (46.6%) of the patients. Mean pulmonary artery pressures (PAP) were 25.03±9.07 mmHg in all cases, 32.9±6.8 mmHg in the group with PH and 18.2±3.5 mmHg in the group without PH. The mean PAP was measured as 28.4±10.0 mmHg in patients diagnosed with IPF, 20.33±6.11 mmHg in patients diagnosed with asbestosis, 18.4±5.17 mmHg in patients diagnosed with sarcoidosis, 27.0±11.3 mmHg in patients with hypersensitivity pneumonitis, and 22.75±4.34 in other patients (one patient diagnosed with nonspecific interstitial pneumonia, one patient diagnosed with lung disease due to rheumatoid arthritis, and two patients diagnosed with pneumoconiosis). The demographic characteristics of the patients, symptom durations, arterial blood gas analysis results, respiratory function test and diffusion test results, 6MWT results are summarized in Table 1, right heart catheterization results are summarized in Table 2. Presence of PH in terms of ILDs diagnoses are summarized in Table 3.

Tablo-1. The demographic characteristics of the patients with or without PH symptom durations, arterial blood gas analysis results (pO2, oxigene saturation, pCO2, pH), respiratory function test and diffusion test results, 6MWT results

| | PH (-) | PH (+) | p value |
|---|---|---|---|
| Age (years) | 60±12 | 63±14 | |
| Gender<br>Female<br>Male | <br>9 (56,2%)<br>7 (43.8%) | <br>6 (42,9%)<br>8 (57.1%) | |
| Symptom durations(months) | 20.7±13.6 | 41.2±36.8 | 0.047 |
| pO2(mmHg) | 68±8 | 53±10 | <0.001 |
| Oxygene saturation (%) | 94±2 | 88±5 | <0.001 |
| pCO2 (mmHg) | 35±4 | 37±7 | 0.406 |
| pH | 7.44±0.03 | 7.46±0.04 | 0.269 |
| %FEV1 | 73,5±12,43 | 52±13,20 | <0.001 |
| %FVC | 67,0±11,56 | 49,5±13,95 | 0.001 |
| FEV1/FVC | 88,5±11,40 | 89,1±11,32 | 0.890 |
| %DLCO | 65,3±11,23 | 38,8±13,72 | <0.001 |
| %KCO | 110,4±28,94 | 75,6±37,80 | 0.010 |
| 6MWT distance (meter) | 414,93±40,58 | 260,42±94,94 | <0.001 |
| Desaturation during 6MWT (%) | 7,12±3,48 | 12,44±5,46 | 0.005 |

PH: Pulmonary hypertension, pO2: Oxygene pressure, pCO2: Carbon dioxide pressure, FEV: Forced expiratory volume, FVC: Forced vital capacity, DLCO: Diffusing capacity of the lungs for carbon monoxide, DLCO/VA: Diffusing capacity divided by the alveolar volume, 6MWT: Six-minute walk test)

Table 2. Right heart catheterization results

| | PH (-) | PH (+) | p value |
|---|---|---|---|
| Right atrial pressure (mmHg) | 3.4±2.6 | 6.6±5.3 | 0.050 |
| Right ventricular Pressure (mmHg) | 10.9±3.7 | 19.2±6.4 | <0.001 |
| Pulmonary arterial pressure | 18.2±3.5 | 32.9±6.8 | <0.001 |
| Pulmonary capiller wedge pressure | 6.5±2.9 | 9.4±2.7 | 0.009 |

To determine the presence of pulmonary hypertension, ROC analysis was used to determine cut-off values for FEV1%, FVC%, DLCO%, DLCO/VA%, 6MWT distance and the desaturation during the 6-MWT Table 4.

Multiple logistic regression analysis was performed. 6MWT distance, desaturation, FEV1%, FVC%, DLCO%, DLCO/

VA% variables were included in the analysis. Among the parameters examined, the most valuable variable in terms of determining pulmonary hypertension was found to be FEV1%. A weaker correlation was detected between the six-minute walk test distance and PH.

Table 3. Presence of pulmonary hypertension in terms of interstitial lung disease diagnoses

| Final Diagnosis | PH (-) | PH (+) |
|---|---|---|
| Idiopathic pulmonary fibrosis (n=15) | 6 | 9 |
| Sarcoidosis (n=5) | 4 | 1 |
| Hypersensitivity pneumonitis (n=3) | 0 | 3 |
| Asbestosis (n=3) | 3 | 0 |
| Others (n=4) | 3 | 1 |

Table 4. Specificity and sensitivity of cut-off values for FEV1%, FVC%, DLCO%, DLCO/VA%, 6MWT distance and desaturation

| Parameter | Cut-off value | Specificity (%) | Sensitivity (%) |
|---|---|---|---|
| FEV1% | 70 | 75 | 92.9 |
| FVC% | 50 | 93.7 | 71.4 |
| DLCO% | 53 | 87.5 | 85.7 |
| DLCO/VA% | 70 | 100 | 57.1 |
| 6MWT distance (meter) | 330 | 100 | 78.6 |
| Desaturation (%) | 9.5 | 80 | 71.4 |

FEV: Forced expiratory volume, FVC: Forced vital capacity DLCO: Diffusing capacity of the lungs for carbon monoxide, DLCO/VA: Diffusing capacity divided by the alveolar volume, 6MWT: Six-minute walk test)

## DISCUSSION

In this study, the clinical findings, respiratory functions and exercise capacities of 30 patients followed with the diagnosis of interstitial lung disease were evaluated, and the data of the cases with and without pulmonary hypertension detected as a result of right heart catheterization were compared. Pulmonary hypertension was determined by right heart catheterization in 14 (46.7%) of the 30 patients included in our study. In previous studies; It has been reported that pulmonary hypertension can be determined between 6-74% in sarcoidosis 5 and 3-86% in idiopathic pulmonary fibrosis.[6]

In interstitial lung diseases, pulmonary hypertension can develop without hypoxemia, but hypoxemia is frequently observed.[7] In our study, consistent with this information, the average $PaO_2$ was found to be 53 mmHg in the group with PH and 68 mmHg in the group without PH. Likewise, the average oxygen saturation was found to be 88% in the group with PH and 94% in the group without PH. This difference was found to be statistically significant.

In cases with interstitial lung disease, a decrease in respiratory function test parameters and diffusion capacities occurs, especially when fibrosis develops. Decreased DLCO indicates fibrosis of alveoli in patients with ILD and PH, respectively. The worsening of the DLCO value despite preservation of lung volumes should suggest the possibility of pulmonary vascular resistance.[8] In our study, FEV1%, FVC%, DLCO%, DLCO/VA% values of the cases were compared and the relationship of these values with the development of pulmonary hypertension was examined. Cut-off values were calculated using ROC analysis. The cut-off value for DLCO% in determining pulmonary hypertension was found to be 53%. The sensitivity of this value was found to be 85.7% and the specificity was 87.5%. Several studies have suggested that DLCO ranging from 30% to 45% can predict PH.[9-11] For the FVC% value, 50% was found to be the critical value in determining pulmonary hypertension. The sensitivity of this value was found to be 93.7% and the specificity was 71.4%. As a result, hypoxemia detected in low DLCO, FVC and deoxygenated blood gas is associated with a high probability of pulmonary hypertension. A disproportionate decrease in DLCO compared to FVC should prompt the clinician to consider the possibility of pulmonary hypertension.

In patients with interstitial lung disease, exercise limitation detected in exercise testing indicates pulmonary vascular changes better than respiratory function parameters.[12] A decrease in the six-minute walk test distance brings with it a decrease in the quality of life and mortality. Studies have shown that even minimal decreases in the 6-minute walk test result in statistically significant changes in patients' clinical conditions.[13] Many studies have shown that the 6MWT distance of ILD patients with PH is lower than that of ILD patients without PH.[14] In a study conducted on patients diagnosed with sarcoidosis, a lower 6MWT distance was found in the group with pulmonary hypertension compared to the group without it (280 meters versus 408 meters), and this statistically significant difference was found to be associated with quality of life and Saint George questionnaire.[15] In our study, exercise capacity limitation in people diagnosed with pulmonary hypertension and followed up with a diagnosis of interstitial lung disease was investigated. For this purpose, a 6-minute walk test was applied to the patients. A statistically significantly lower 6MWT distance was detected in the group with pulmonary hypertension. By calculating the threshold value for the 6-minute walk test distance using ROC analysis, it was aimed to predict pulmonary hypertension and reveal the need for further examination in patients followed with a diagnosis of interstitial lung disease. For the six-minute walk test distance, the value of 330 meters was found to have 78.6% sensitivity and 100% specificity. In a study evaluating tools that could predict the development of pulmonary hypertension in interstitial lung disease, this value was predicted to be 350 meters sarcoidosis.[5] In the study of Cahalin et al.,[16] which evaluated cases diagnosed with interstitial lung disease in need of transplantation, it was observed that the risk of developing pulmonary hypertension increased in cases with a 6-minute walking distance below 300 meters.

In this study, to determine hypoxemia during exercise, saturation records were taken during the 6-minute walk test and the lowest values detected at the beginning and during the test were compared. Hypoxemia was observed more clearly during exercise in the group with pulmonary hypertension. As a result, desaturation of more than 9.5% during the test was found to be associated with the development of pulmonary hypertension. Similarly, previous studies have reported that a decrease of more than 10% in saturation during the 6-minute walk test in patients with pulmonary hypertension may be a determinant of mortality.[17]

As a result of multiple logistic regression analysis, it was determined that among the expected FEV1%, expected FVC%, expected DLCO%, expected DLCO/VA%, 6MWT distance and desaturation parameters during 6MWT, the most valuable parameters to predict pulmonary hypertension in interstitial lung diseases were expected FEV1% and 6MWT distance. However, due to the small number of cases, the relationship between these values and the degree of pulmonary hypertension could not be examined. In a study by Bourbonnais and Samauati[18] evaluating patients with sarcoidosis, the expected DLCO%, 6MWT distance and desaturation during the test were found to be related to pulmonary hypertension, but the strongest predictor was the desaturation detected during the 6-minute walk test.

### Limitaitons

Our study had some limitations. A small number of cases from many disease groups were included in the study. For this reason, evaluations regarding disease subgroups could not be made. The small number of cases in some disease groups was insufficient for comparison and statistical analysis. Since the follow-up period of the cases was not long (one year), the relationship between the development of pulmonary hypertension and mortality and morbidity could not be examined.

## CONCLUSION

Cases diagnosed with interstitial lung disease with a decrease in respiratory function tests and exercise capacity should be investigated for pulmonary hypertension if there is clinical suspicion. If necessary, the diagnosis should be confirmed with right heart catheterization, which is the gold standard diagnostic method.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was carried out with the permission of Eskişehir Osmangazi University Faculty of Medicine Ethics Committee (Date: 31.08.2010, Decision No: 2010/165).

### Informed Consent

All patients signed and free and informed consent form.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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